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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,732	12/01/1999	ALVIN H. SCHMAIER	8820-3	6339

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EXAMINER	
GUPTA, ANISH	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 07/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/402,732	SCHMAIER ET AL.	
	Examiner	Art Unit	
	Anish Gupta	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4-28-04*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 14-28* is/are pending in the application.

4a) Of the above claim(s) *26-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 14-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants amendment filed, 4-28-04, is acknowledged. Claims 1, 3, 14 and 16 were amended. Claims 11-13 were canceled. Claims 1-10 and 14-28 are pending in this application and claims 26-28 have been withdrawn for the reasons in the previous office action and the reasons set forth below.

Election/Restrictions

2. Applicant's election of Group I and II in the reply filed on 11-5-02 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

This application contains Group II, claims 26-28 drawn to an invention nonelected without traverse in the reply filed on 11-5-02. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-10 and 14-25 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants argue that "each segment" refers to a compound where there is more than one segment, i.e. the compound is a multimer. However, is unclear from the claim that the "each segment" refers to the multimer. "Each segment" can also make reference to the segment of X1 and a different segment of X2. The claims, therefore, remain indefinite.

For this reason, the rejection is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-10 and 14-25 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the analogs of SEQ ID 6, SEQ ID 7, the peptide RPP, the peptide RPP MAP-4 and the peptide RPP heterodimer for inhibiting thrombin induced platelet aggregation, does not reasonably provide enablement for all of the compounds claimed in the claims and inhibition of "other cell activation." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons set forth in previous office action and the reasons set forth below.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8)

the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

Applicants argue that the reference relied upon in the rejection do not cast doubt with respect to the enablement of the claimed invention. Applicants state that Ngo et al. discusses the complexity of mathematical methods to predict folding of proteins. This reference does "not asset that preparing peptides and testing their biological activity is no routine in the art." For Rudinger, the term "painstaking experimentation" is not synonymous with "undue experimentation." Applicants rely on a ordinary dictionary definition that states that "painstaking" is careful or diligent experimentation but not undue. Further, Applicants state that Rudinger does not support the contention that that the peptide art is unpredictable. "Rudinger in fact demonstrates that at the time the application was filed, it was routine for one of ordinary skill in the art to prepare and test compounds comprising peptides of various sequences having a desired biological function." Finally, Applicants argue that Hasan et al. teaching with respect to AD-induced activation is moot in light of the amendment to the claims. Moreover, the RPPGF sequence disclosed by Hansan is not applicable to the claimed invention since the N-terminal amino acid of X2 cannot be glycine.

Applicants state that the "specification not only describes methods for preparing and testing peptides of various sizes, the specific anti-thrombin peptides described above comprise lengths of 3, 5, 8, and 16 amino acids in size, including various branched peptides." Thus, based on the teachings of the specification and the knowledge available at the time the application was filed, one of ordinary skill in the art would have been able to synthesize compounds according to the claims, including those peptides corresponding to the branched peptides. Applicants state it is no more than "routine" experimentation is needed to test

compounds prepared as described in the specification, since assay methods can be combined to measure peptide inhibition of thrombin induced cell activation. Thus, "[t]he specification provides multiple examples of peptides with the ability to inhibit thrombin-induced activation and provide adequate guidance for preparing and testing additional compounds for use in inhibiting the claimed thrombin-induced activation."

Applicant's arguments filed 4-28-04 have been fully considered but they are not persuasive.

First, it is believed that Hasan, even though Applicants have amended the claims to recite thrombin-induced cell activation, is still pertinent to establish the unpredictability of activity with respect to peptide sequences. The addition of a single amino acid, such as glycine can have adverse effects on the activity. Applicants claims describe peptides that have only three amino acids, but can have up to 63 amino acids. Given the deleterious effects of a single amino acid, one actually has to make each amino acids sequence and test them to determine activity. It is no enough that to concluded that since the peptide has the amino acid sequence Arg-Pro-Pro it will automatically be effective in inhibiting thrombin-induced cell activation. Both Rudinger and Ngo et al echo this sentiment. Given the complex mathematical formulation for protein folding, as Applicants acknowledge, one cannot conclude how a given peptide will be have when drawn out on paper, since the protein will fold. Thus one has to make the peptide and test the peptide for activity. Similarly, Rudinger, stands for the proposition that one can conclusively state that a single amino acid change will not alter activity. Rather, the significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking, or as Applicants state diligent,

experimental study. Thus, given the teachings of the references, one must determine the activity for each peptide before conclusive statements can be made with respect to activity.

Applicants assert that experimentation to practice the claimed invention or determine the inhibition of thrombin activity is by no mean "undue" but merely "routine" since assay methodology is disclosed to determine active and inactive peptides. In the spirit of Applicants response, a dictionary definition as been utilized to define "undue." Undue is defined as "exceeding the appropriate or normal: EXCESSIVE." (see Webster's II, New Riverside University Dictionary, copy enclosed). The claims state that the compounds has the formula X1-Arg-Pro-Pro-X2 and L-(X1-Arg-Pro-Pro-X2)n, where X1 and X2 are up to 30-amino acids that are natural or synthetic and n is between 2 to 20. Using the most conservative calculations, involving the linear peptide and X1 and X2 as natural amino acids, the peptides are inclusive of peptides up to 60^{20} possible combination of peptides that have up 30 natural amino acids. That is, if on of ordinary skill in the art wants to determine the peptide that have 30 naturally occurring amino acids for each X1 and X2 that are able to inhibit thrombin-induced cell activation, one has to make 3.656×10^{35} peptides and then utilize assay methods to determine activity. This figure does not include any peptides where X1 is between 1-29 or X2 is between 1-29 amino acid peptide and where the X1 and X2 include synthetic amino acids or those branched peptides encompassed by the claims. Indeed given the breath of the claims, the number of different peptides encompassed by the claims is astronomical, far greater than the conservative number of 3.656×10^{35} peptides calculated above. It is not as "routine" as making a handful of peptide analogs and determining activity using known assay methods. Rather, one of ordinary skill in the art ahs to make every one of these peptides and testing everyone of these peptides for activity as encompassed by the claims. This experimentation is by no means "routine." It is

"excessive" and thus "undue" (emphasis added). As stated above, it is not sufficient to state that since a 63 amino acid peptide contains the sequence Arg-Pro-Pro- it will be active in inhibiting thrombin induced cell activation.

In Amgen, Inc. v. Chugai Pharmaceutical Co. LTD., 927 F.2d 1200, 18 USPQ 2d 1016 (Fed. Cir. 1991), the court held a generic claim covering all DNA sequences that would encode a protein sufficiently duplicative of EPO that it had the property of increasing the production of red blood cells as nonenabling. The court stated:

> "Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, with attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity. Under the circumstances, we find no error in the court's conclusion that the generic DNA sequence claims are invalid under Section 112." Id. at 1214.

Here, like in Amgen, Applicants are claiming a generic peptide sequence that define three amino acids but can be up to 63 amino acids in a linear fashion. The structural complexity and possible permutations are enormous. Applicants have made disclosed only handful of different peptides that are similar in structure and size which are not commensurate in scope of the claims. Although Applicants have stated in their response that several branched peptides are disclosed, the specification only discloses the activity for RPP MAP-4 branched peptide and RPP tri-peptides. The specification does not have a single branched peptide that have between 5-20 branches which have up 60 amino acids in each branch. Thus one is burdened with undue, or excessive, experimentation to practice the claimed invention.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

1. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (571)272-0965. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell , can normally be reached on (571) 272-0974. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bruce Campell

7/9/04

Anish Gupta
Patent Examiner

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